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Systematic Review and Meta-Analysis of TST Conversion Risk in Deployed Military and Long-Term Civilian Travelers

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Background. Transmission of tuberculosis (TB) during travel is a significant potential infectious disease threat to travelers. However, there is uncertainty in the travel medicine community regarding the evidence base for both estimates of risk for latent TB infection (LTBI) in long-term travelers and for information regarding which travelers may benefit from pre- or post-travel TB screening. The purpose of this study was to determine the risk for tuberculin skin test (TST) conversion, used as a surrogate for LTBI, in long-term travelers from low- to high-risk countries.

Methods. We performed a systematic review to acquire all published and unpublished data on TST conversion in long-term civilian and military travelers from 1990 to June 2008. Point estimates and confidence intervals (CIs) of the incidence of TST conversion were combined in a random effects model and assessed for heterogeneity.

Results. The cumulative risk with CI for LTBI as measured by TST conversion was 2.0% (99% CI: 1.6%–2.4%). There was a marked heterogeneity (χ^2 heterogeneity statistic, $p < 0.0001$) which could not be explained by evaluable study characteristics. When stratifying by military and civilian studies, the cumulative risk estimate was 2.0% (99% CI: 1.6–2.4) for military and 2.3% (99% CI: 2.1–2.5) for civilian studies.

Conclusion. The overall cumulative incidence of 2.0% is what could be expected to occur among the local population in many developing-country settings, though TST conversion likely overestimates the risk of TB infection because of the low positive predictive value (PPV) of the TST in low-prevalence populations such as travelers. To maximize the PPV of a screening test for LTBI, a targeted testing strategy for long-term military and civilian travelers is recommended, based on exposures known to increase the risk of TB. Studies to better define higher risk groups, activities, and locations are needed.

Tuberculosis (TB) infection and transmission remain one of the greatest public health threats worldwide. Although the prevalence of TB has greatly decreased in the temperate and developed nations of Western Europe, North America, Australia, and Japan, it remains a major disease burden in tropical and developing countries.[1,2] Consequently, travelers and expatriates from low-prevalence nations who travel or live in high-prevalence nations may become infected with TB.[3] In the travel medicine community, however, there is debate about the risk for latent tuberculosis infection (LTBI) that results from long-term travel.[4,5]

Cobelens and colleagues suggested that the risk to travelers of acquiring LTBI is similar to that of the general population in the destination country.[3] A study among Peace Corps Volunteers from 1996 to 2005 reported an annual infection risk of 0.8% to 1.2% and an active TB incidence density of 68.9 per 100,000 volunteer-years,[6] somewhat higher than that for the population of Brazil in 2006 (50/100,000/year).[7]

In contrast, Rieder suggested that many apparent latent TB infections in travelers from low-incidence countries to high-incidence countries may be due to false positive tuberculin skin tests (TSTs) in this otherwise low-prevalence population.[5] Pseudoepidemics of TST conversions in military populations have been reported in relation to travel,[8] as well as in non-traveling civilian populations.[9–11] Although the TST is the most well-studied test we have to date to detect the presence of LTBI, it is not a "gold standard" because it is currently impossible to know if a person is latently infected with a few viable *Mycobacterium tuberculosis* organisms. Due to the inherent relationship between positive predictive value (PPV) and prevalence of infection, many TST conversions may actually be false positives in a low-risk

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travel population. Thus, the PPV of a TST conversion in low-risk travelers is probably less than 50%, and may be as little as 16% in the absence of a known exposure to TB.[12]

As a result of these conflicting estimates of risk and the inherent limitations of the TST, there is uncertainty as to the value of TST screening among long-term travelers, which leads to variability in screening policies and recommendations. The US Centers for Disease Control and Prevention (CDC) recommend both pre- and post-travel testing, but only for travelers who will come into routine contact with high-risk populations, such as hospital patients, the homeless, and prisoners, as well as travelers who anticipate extended travel or frequent repeat trips to high-risk areas.[13] Travax travel medicine software (Shoreland, Inc., Milwaukee, WI, USA) recommends that "travelers to countries with high risk (ie, >100 cases per 100,000) should have pre-departure testing if staying for >1 month; travelers to countries with moderate risk (approximately 25–100 cases per 100,000) should have pre-departure testing if they plan on staying for >3 months."[14] Previously, Canadian public health guidelines suggested that travelers going to high-risk countries for 3 months or more should be tested.[15] Current Canadian public health guidelines now recommend a single, post-travel test based on duration of travel as well as TB incidence in the country visited.[16] Finally, some recommend foregoing testing altogether, since infection is rare and false positive skin tests common in low-prevalence populations.[5]

There is even more variability in screening policies among military than among civilian groups. Many militaries, including those of Germany and Canada as well as the US Army,[17] have regularly tested their service members before and after overseas deployments to detect possible LTBI acquired during travel, although the US Army has recently revised this policy.[18] Although exposures are heterogeneous, military members may engage in activities which create a higher risk for TB infection, such as humanitarian assistance and health care operations serving local, high-risk populations.[19–21] Other militaries, such as those of the British and Dutch, perform no TB testing. The US Navy tests operational units yearly and all others every 3 years,[22] whereas the US Air Force began targeted post-deployment testing of deployed airmen in 2005 based on a risk factor questionnaire.[23]

These inconsistent policies are in large part due to the uncertainty regarding risk for LTBI among long-term travelers. The purpose of this study was to estimate the risk for LTBI, as measured by TST conversion, in long-term military and civilian travelers from low- to high-risk countries. Making the best estimate of incident LTBI in these populations will provide data to guide and support policy recommendations.

Methods

A systematic literature review was performed with the assistance of a research librarian at the Uniformed Services University of the Health Sciences (USUHS) to acquire all available data published on TB infection risk in travelers and deployed military personnel. The three databases of PubMed Medline, Current Contents Connect, and EMBASE were searched for publications between January 1, 1990, and June 1, 2008, inclusive, using the following search criteria: Medline—"Tuberculosis"[Majr] And "Travel"[Majr], EMBASE—'tuberculosis'/mj and 'travel'/mj and [english]/lim and [humans]/lim and [embase]/lim, Current Contents Connect—(tuberculosis OR TB) and travel*. In addition, we reviewed bibliography reference lists and abstracts for papers not captured by the electronic database searches.

We found 344 published papers that met our search criteria. Two of the authors (RF and JM) independently reviewed the selected papers for those appropriate for inclusion in our meta-analysis, restricting papers with titles or abstracts inappropriate for the focus of our study, those published in languages other than English, case reports and editorials, topic reviews, and studies of travelers who did not originate from low-prevalence countries.

Studies which were determined to be appropriate were retrieved for review. Eligibility criteria for inclusion and extraction were those studies since 1990 examining risk for TB infection among military and civilian travelers from low-prevalence countries traveling for more than 1 month, and with data available for extraction. Although studies using interferon-gamma release assays (IGRAs) were not specifically excluded from the analysis, the only study using an IGRA in a travel population was among travelers from a high-prevalence country, Indonesia.[24] Since Indonesia is a high-risk country of origin, with an incidence of active TB exceeding 200 per 100,000 per year,[25] it was excluded from the analysis.

We also searched for unpublished civilian and military surveillance data in conference proceedings, military medical databases, and through personal communications with civilian and military public health experts. Conference proceedings of the Infectious Diseases Society of America and the American Society of Tropical Medicine and Hygiene were reviewed. We also queried the US Department of State, the US Army Special Operations Command (including Civil Affairs), the militaries of the United Kingdom and the Netherlands, as well as multinational corporations for TB testing data. TB testing results from deployed personnel of the Canadian and German Armed Forces were obtained by personal communication (Dr Paul C. LaForce, January 2008; Dr Ingo Fengler, January 2008).

Data on TB testing among US Army and US Air Force personnel were obtained with permission from

the electronic immunization registries MEDPROS (Medical Protection System) and AFCITA (Air Force Complete Immunization Tracking Application). These databases record information from US Army and Air Force TST and immunization activity. This information is entered regularly by technicians or health care providers when units receive their deployment-related or periodic TSTs or immunizations.

The primary outcomes of cumulative incidence and incidence density were obtained directly from the published estimates. Outcome data were extracted by two independent reviewers (RF and JM), and derived calculations using incident cases and person-time denominator were verified by comparison with each other and with the data reported by study authors. Other variables extracted included year and location of travel and source population characteristics.

Analyses were conducted by use of Stata v.10 (StataCorp LP, College Station, TX, USA). In addition to descriptive statistics on the included studies, meta-analysis was employed to pool risk estimates (cumulative incidence and incidence density) using a random effects model by the method of DerSimonian and Laird.[26] We used 99% confidence intervals to assure more robust estimates of risk. Risk (cumulative incidence) was defined as the number of conversions divided by the total number of travelers at risk. Incidence density rate was defined as the number of infections divided by the total person-time at risk. Person-time for those infected was halved, since infections were assumed to have occurred halfway through the travel time, on average. Heterogeneity was assessed graphically using Forest plots and statistically using the chi-square test for heterogeneity.[27]

Heterogeneity was explored by the use of multiple subgroup analyses to determine any differences of estimates through stratification. We also conducted a meta-influence analysis to determine if there were any overly influential studies.[28] Scatter plots were used to examine the association of incidence with average duration of travel. Other potential associations for differential risk were assessed, including region of travel, unpublished versus published studies, civilian versus military studies, and other risk factors and source population characteristics. Quality scoring based on criteria adapted from Seidler and colleagues was also conducted.[29] Only one study by Cobelens and colleagues had sufficient information to calculate a quality score, and this was also the only prospectively performed study. Studies from which the other estimates were obtained were retrospective, with data routinely collected for surveillance purposes. Therefore, analysis of study quality was done by comparing the single prospective study with the others based on surveillance data.

Results

Out of 344 published studies identified through electronic databases and bibliography reference lists, 5 articles fulfilled all eligibility criteria and were abstracted. The search for unpublished civilian and military data resulted in the inclusion of four additional data sources in the analysis (Figure 1).

Table 1 describes the nine included data sources. Studies were conducted between 1995 and 2007. Seven of the nine estimates were obtained from military populations, with the remaining two among civilian travelers. The median travel time among the nine studies was 11 months, with an interquartile range of 7 to 10.5 months (range 4–18 months). The locations of travel were fairly heterogeneous, as three of the nine (two civilian and one military) included various worldwide travel destinations. However, military deployment locations were over-represented, with five populations traveling predominantly to Southwest Asia (SWA) or the Balkans. Most travel to SWA consisted of deployments to Iraq and Afghanistan. Travel to the Balkans consisted primarily of deployments to Bosnia-Herzegovina. The remaining military population had contact only with Haitians on US Naval Base Guantanamo in Cuba.

Our analysis resulted in an estimated overall cumulative incidence of LTBI among long-term travelers from low-prevalence countries, as measured by TST conversion, of 2.0% (99% CI: 1.6–2.4) (Figure 2). Estimates of cumulative incidence among the nine studies and data sources ranged from 0.96% to 3.59%. The overall incidence density was 2.9 conversions per 1000 person-months (99% CI: 2.5–3.4). The cumulative incidence scatter plot shows that the risk of conversion was relatively constant over the average duration of travel seen in the studies (Figure 3). In contrast, the incidence density scatter plot appears to demonstrate a decrease in conversion rates as average travel duration increased (Figure 4). Calculation of an incidence density rate assumes that the rate of infection is constant over the interval studied, but the data in Figure 4 violate that assumption. Therefore, the remaining analyses use only the cumulative incidence measures.

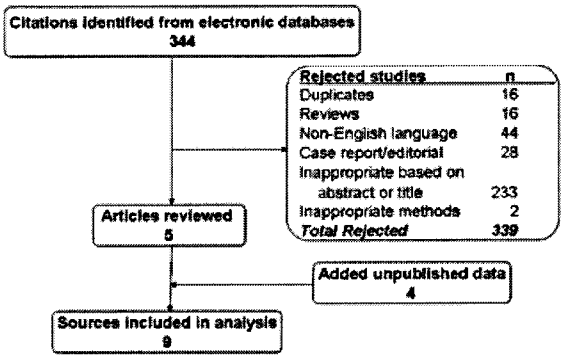

Figure 1 Flow diagram of study selection for inclusion in meta-analysis.

Table 1 Characteristics of included studies

Author	Study dates	Number tested	Number converted	Percent converted	Average person-years of travel	Conversion rate/100 person-years	Average person-months of travel	Conversion rate/1000 person-months	Timing of tuberculin skin testing	Purified protein derivative used	Travel location
German military	2003–5/2007	6,675	191	2.86	0.33	8.7	3.94	7.25	Pre- and post-deployment	PPD RT 23	Bosnia, Georgia, SW Asia
Cobelens et al.[3]	1995–1997	656	12	1.83	0.43	4.2	5.19	3.50	Pre- and post-travel	*M. tuberculosis*, *M. scrofulaceum*	Worldwide
Emmons et al.[21]	1995–1997	11,049	224	2.03	0.49	4.1	5.94	3.42	Prior to accession and pre- and post-deployment	Aplisol, Tubersol	Bosnia
Kortepeter et al.[20]	1995	1,280	46	3.59	0.49	7.3	5.89	6.08	Prior to accession and pre- and post-deployment	Aplisol, Tubersol	Haiti
Bowman et al.[30]	1999–2002	1,190,866	17,493	1.46	0.99	1.5	11.91	1.25	Prior to accession and post-deployment	Aplisol, Tubersol	Worldwide
US Army	2003–2007	972,495	9,329	0.96	1.00	1.0	11.94	0.83	Prior to accession and pre- and post-deployment	Aplisol, Tubersol	SW Asia
Jung et al.[6]	1996–2005	44,070	1,028	2.33	1.50	1.6	17.98	1.33	Pre- and post-travel	Aplisol, Tubersol	Worldwide
Canadian military	6/2004–2006	4,441	104	2.34	0.49	4.8	5.93	3.95	Pre- and post-deployment	Tubersol	Bosnia, SW Asia
US Air Force	2002–2007	72,721	1,469	2.02	0.33	6.1	3.96	5.08	Prior to accession and targeted post-deployment	Aplisol, Tubersol	SW Asia

SW Asia = Southwest Asia.

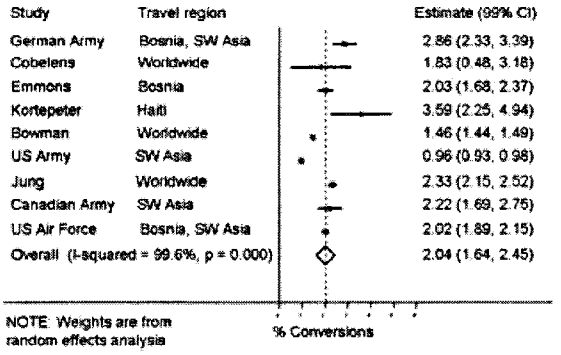

Figure 2 Cumulative incidence risk of tuberculin skin test (TST) conversion in long-term military and civilian travelers.

There was marked heterogeneity among studies estimating cumulative incidence (χ^2 heterogeneity statistic, $p < 0.0001$). Attempts to explain this heterogeneity for most variables was limited due to the small number of studies in each subgroup and limited data on other risk factors for TB infection, but stratification was used to explore this heterogeneity to the extent possible. Examination of meta-influence (not shown) suggested that no single study substantially affected the overall estimate. Exclusion of the large US Army data set from MEDPROS and the Navy study by Bowman increased the cumulative incidence estimate to 2.3% (99% CI: 2.0–2.7).[30] When stratifying by military or civilian studies, the cumulative incidence risk estimate was 2.0% (99% CI: 1.6–2.4) for military studies and 2.3% (99% CI: 2.1–2.5) for civilian studies. Stratifying the analysis by published and unpublished studies resulted in a cumulative incidence of 2.0% (99% CI: 1.6–2.4) for published studies and 2.0% (99% CI: 1.0–3.1) for unpublished studies. Stratifying by travel to recent conflicts in SWA only versus travel elsewhere resulted in an estimated cumulative incidence of 1.7% (99% CI: 0.6–2.9) for data from SWA and 2.3% (99% CI: 1.6–3.0) from all other locations. Stratifying by deployments from North America (United States and Canada) versus deployments from other countries resulted in a cumulative incidence of 1.9% (99% CI: 1.5–2.4) for North America and 2.5% (99% CI: 1.2–3.8) for others. Finally, temporal trends were considered by stratifying the analysis by data sources which only contained military data after 2001, which marked the beginning of Operation Enduring Freedom (OEF) combat operations in Afghanistan, compared to those civilian and military sources obtained prior to 2001. This resulted in estimates of 2.0% (99% CI: 1.0–3.1) for data after 2001 and 2.1% (99% CI: 1.4–2.9) for data sources including travel from before 2001.

Discussion

Our systematic review of nine published and unpublished studies and data sources of LTBI in long-term travelers resulted in an overall pooled estimate of 2.0% cumulative incidence, as measured by TST conversion after travel. Although estimates varied considerably from one study to another, stratified estimates were similar. In particular, cumulative incidence varied little between military and civilian travelers (2.0% vs 2.3%) despite the heterogeneous nature of activities in which civilian travelers and deployed military units engage. Our pooled risk estimate of 2.0% is similar to the risk seen in the only prospective published study (Cobelens et al., 1.8%).[3]

To our knowledge, this is the first comprehensive effort to determine a pooled estimate of TST conversion, used as a surrogate for risk for LTBI, among long-term travelers. Because we were able to obtain both published and unpublished data from a

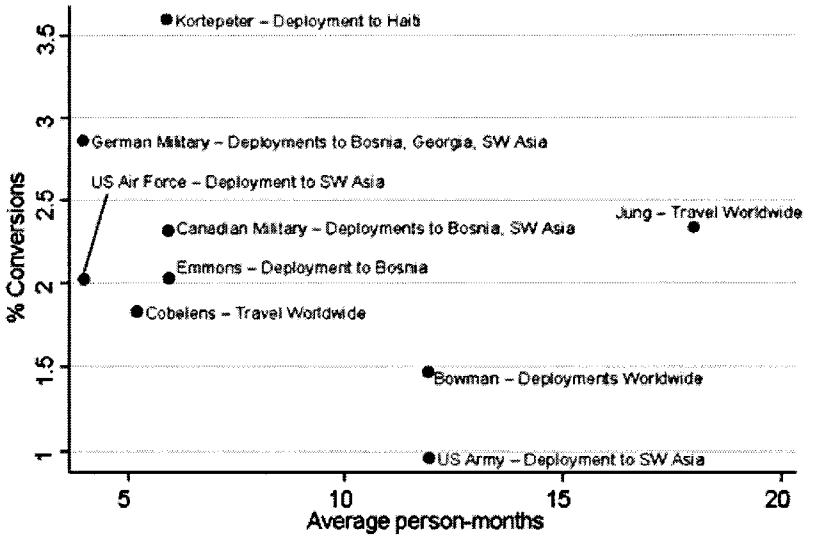

Figure 3 Cumulative incidence scatter plot of tuberculin skin test (TST) conversion in long-term military and civilian travelers.

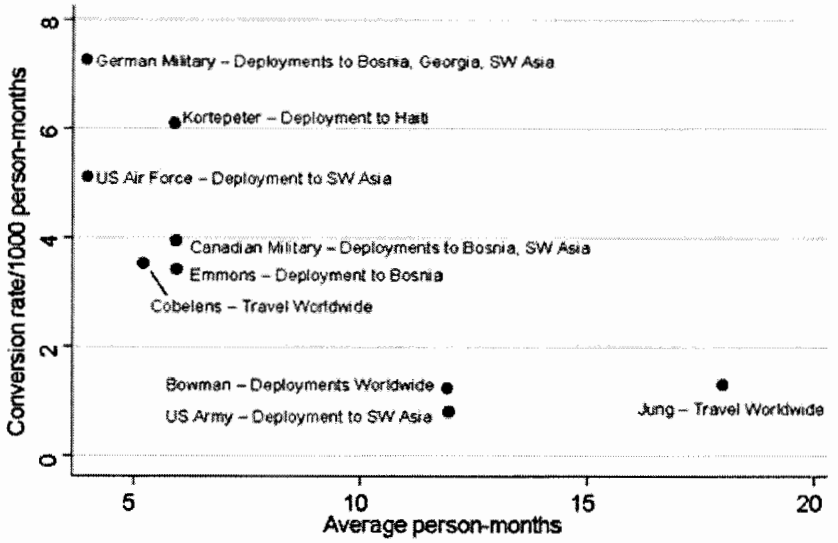

Figure 4 Incidence density scatter plot of tuberculin skin test (TST) conversion in long-term military and civilian travelers.

variety of military and civilian sources, we believe that we have captured a robust sample of travel experiences, increasing our confidence in the applicability of our estimate to similar populations. Our comprehensive search strategy with various overlapping approaches enabled us to retrieve relevant studies and surveillance data collected systematically since 1990. Finally, two reviewers independently completed screening and study selection, increasing the reliability of the estimates.

The differences between deployed military members and long-term civilian travelers may lead to concerns about generalizability of these results. However, the stratified estimates of military and civilian risk for infection were similar. Additionally, while military personnel are different in many ways from civilian populations, military exposures to local populations during deployment often approximate those of civilian travelers. For example, many long-term civilian business and vacation travelers may stay in hotels and resorts, except for transient trips out into the surrounding area for sight-seeing, activities, and shopping. Similarly, many military personnel stay on secured bases except for transient trips out into the surrounding area for patrols and operations. These are probably low-risk situations for most members of these populations because of limited contact with infectious individuals. Conversely, both civilian aid workers and military personnel may engage in humanitarian assistance operations and work in health care settings among populations with a potentially high prevalence of disease. Close exposure of many Peace Corps Volunteers to local populations is paralleled by the exposure of members of military Provincial Reconstruction Teams and Civil Affairs and Special Operations units, who also often live in the communities and among the populations with whom they work.

It appeared from our incidence density results that the data violated the assumption of a constant rate of infection over time, as evidenced by an apparent decrease in conversion rates as average travel duration increased. There is a general agreement that the greater the length of time spent in close contact with high-risk populations, the greater the risk of latent TB infection.[31,32] Cobelens and colleagues found that a cumulative history of more than 3 months of travel to high-incidence areas increased the risk for LTBI.[33] Our incidence data, however, did not show a positive association between rate of LTBI and average duration of travel. In fact, cumulative incidence of TST conversion was highest in the German military (2.9%) and in US military personnel participating in humanitarian operations (3.6%).[20] Both of these groups had shorter durations of travel (<6 months) than other study populations with lower cumulative incidences, such as Peace Corps Volunteers (1.3%), most of whom serve for 27 months and many of whom live with local families in the host country. These counterintuitive results may be due to heterogeneous risk within these populations from differences in activities and exposures. Alternatively, in some settings the majority of risk for infection may accrue early in travel. However, given the heterogeneous nature of settings, populations, and activities, and the nature of this meta-analytic study, we were unable to determine causal relationships.

Though cumulative incidence of LTBI has been documented to be higher among US forces serving in high-incidence geographic areas[30,34] and on a humanitarian assistance mission among a high-risk Haitian population, some of the results of this study differ from what would be expected based on those outcomes. The cumulative incidence of LTBI in German and US forces deployed to Bosnia (2.9% and 2.0%, respectively) was higher than those of US

forces deployed predominantly to Iraq and Afghanistan (1.7%), though the rates of TB among the local population are substantially higher in Afghanistan, and rates are as high in Iraq as they are in Bosnia.[25] These differences in rates of TST conversion may, among other possible causes, be due to underreporting in US forces deployed to these regions or a lower intensity of exposure to TB among US forces. The latter could have occurred prior to the "surge" of troops into Iraq in 2007 because the well-known danger of travel off-base from improvised explosive devices (IEDs) resulted in many US forces being isolated and kept on US military bases away from close contact with the local population.

The risk of being infected by TB depends on the degree of TB exposure during travel, not simply the travel itself or its duration. TB exposure is affected by many factors, including the prevalence of TB infection in the population to which one is exposed, the presence of an infectious source, the density of droplet nuclei in the air, the duration of exposure to that air, the quality of air filtration in removing infectious droplets, whether the exposure is indoors or outdoors, and host immunological and mechanical factors.[5,35,36] Certain categories of travelers therefore may be considered at greater risk for infection based on greater potential exposure to TB-infected populations. These include health care workers,[3,37] those in contact with prison populations,[38] and those visiting friends and relatives or the children of such travelers.[39]

The Peace Corps Volunteers and the soldiers involved in humanitarian assistance in a refugee setting at Naval Base Guantanamo were populations in which close contact with local nationals may have occurred more frequently. The Peace Corps Volunteers studied had a cumulative incidence of 2.3%, only 15% higher than the overall risk estimate of 2.0%, while that for US soldiers providing humanitarian assistance to Haitian refugees at Guantanamo Bay was 3.6%, almost double the overall estimate, even though Peace Corps Volunteers' exposure to the local population is of long term and that for the soldiers averaged less than 6 months. However, the only characteristic significantly associated with increased risk for TST conversion among the soldiers was birthplace outside the United States. The authors of the Guantanamo study speculate that non-US-born soldiers may have had language skills that may have increased their exposure to refugees with active TB, but also state that it is possible that soldiers whose TSTs were positive before deployment were misclassified as TST converters.

TST conversion can be due to LTBI or can be falsely positive. It is possible that some of the differences in results seen among the studies are due to false positive reactions to the TST from cross-reactions with non-tuberculous mycobacteria (NTM), boosting of waned LTBI or NTM infection, or variability in skin test administration and reading.[8] These limitations of the TST as a diagnostic tool probably result in an overestimate of the true risk of infection. Although we estimate a 2% risk of conversion, plausible values of PPV range from 16% to 50% in US-born populations.[12] With a PPV of 50% this would reduce the estimate to 1%, which is still rather high. Alternatively, with a PPV of 16%, the estimated risk of infection would be 0.33%.

Although boosting of LTBI may be addressed by two-step testing prior to travel, this is very difficult to accomplish in a travel medicine setting. Many of the studies and data sources lack two-step testing, and thus do not take into account the booster phenomenon. Because the German military takes boosting into account by the use of two-step testing, the noticeably higher incidence of TST conversions in deployed German military units (2.9%) is interesting. However, this may be explained at least in part by several factors. Although the German military does not conduct Bacillus Calmette-Guérin (BCG) vaccination during military service, vaccination prior to joining the military may affect TST results, as it is available to the civilian population. Additionally, the Germans use PPD RT 23 (Statens Serum Institute, Copenhagen, Denmark; Dr Roland Köhler, personal communication, June 2008), a different product than is used in the United States and that may have somewhat different operating characteristics. Thus, several factors specific to particular units or individuals, such as exposure to BCG, TB, or NTM, use of a different TST product, or variability in TST administration and reading might account for the higher German incidence of LTBI compared to United States or Canadian military and travelers. Although the US military does not perform two-step testing prior to travel (deployment), all service members are tested upon entry into military service, and all Army and Navy service members are required to undergo testing within 1 year prior to deployment. Thus, military data sources may reflect more boosted reactions than civilian studies, at least on the first test after entry into military service.

Another potential variable affecting estimates of LTBI in travelers is selection bias due to varying rates of adherence to post-travel testing.[5,40–42] Adherence to post-travel testing in civilian populations is often poor, resulting in a possible selection bias, which complicates determination of true travel-associated infection. Due to compulsory testing, military populations may have less selection bias both by having fewer subjects who decline to participate and from fewer losses to follow-up (reading of the test) than is possible in civilian populations. Furthermore, militaries may have more robust electronic administrative record-keeping systems that allow the compilation of large numbers of skin tests related to travel (deployment). On the other hand, military testing is usually done in large numbers, where quality control may not be as rigorous, which occasionally results in the pseudoepidemics mentioned, and may also result in underreporting.[8]

Another significant limitation of this study is that it is not generalizable to all long-term travel populations.

The data sources used in this study over-represented military members, and SWA was by far the most frequent travel destination. Furthermore, the military data sources contained markedly larger population samples than civilian studies, although the meta-influence analysis demonstrated that no single study significantly affected the estimate. However, group characteristics should always be used with caution when assessing TB exposure risks, as individual risks and exposures are of much greater importance. IGRAs may also be used to aid diagnosis of LTBI in place of the TST.[43] However, the only study to assess travel-related TB risk using an IGRA was done in a high-prevalence country of travel origin and so was not included in our analysis.[24] IGRAs are more specific than the TST in BCG-vaccinated populations, but only slightly more specific for LTBI than the TST in populations that have not been vaccinated with BCG.[44,45] There are similar concerns regarding reliability and PPV in low-prevalence populations as for the TST.[46,47] Thus, similar to the TST, IGRAs should be used only in travel populations at significantly increased risk for TB infection, and testing should be carefully targeted based on individual risk factors.

Conclusion

In the heterogeneous populations studied here, the cumulative incidence of LTBI averaged 2.0% (99% CI: 1.6–2.4), as measured by the TST, with a range in individual study estimates from 0.96% to 3.59%. This result was likely influenced by false positives due to the limitations of the TST and the likelihood of false positive test results in a low-prevalence population. To maximize PPV of either the TST or an IGRA, we suggest an individualized risk-based approach, targeting higher-risk, long-term military and civilian travelers based on their duration of travel, the TB endemicity of the country to which they travel, the type of activities in which they will engage, and how closely they will interact with the local population, particularly in an indoor setting. Such targeted testing has already been recommended by the CDC,[13] the Canadian Public Health Agency,[16] and the US Air Force.[23]

Additional studies are needed among international traveler populations to identify more precise population- and individual-level factors that are associated with both differential risk for LTBI and risk of progression to active disease, and that can be both generalized and applied on a regional basis. This type of knowledge would assist in the development of better targeted testing recommendations. Data sources should include travel clinics that service civilian and governmental populations, militaries that deploy outside their home country, and multinational corporations that may have large numbers of expatriates living in nations with a high TB prevalence. Heterogeneous populations should be studied to further explore causes of heterogeneity in risk for LTBI, such as lengths of travel, activities performed, and location of travel. Since the heterogeneity inherent in the population of long-term travelers may be a source of unmeasured confounding, a careful intra- or post-travel exposure assessment and attention to demonstrated risk factors is critical in obtaining an unconfounded estimate of risk. Individual risk factors should be accounted for, such as being foreign-born, visiting friends and relatives, engaging in health care activities, having HIV infection or other immunosuppressive comorbidities, as these populations may be at greatest risk for exposure to or infection with TB. Additional variables that should be measured include infection with NTM and history of BCG vaccination. Prospective testing using two-step TST with comparison IGRA, and including intra-travel and post-travel testing with follow-up to active TB would contribute valuable data but may be resource-intensive and cost-prohibitive.

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Declaration of Interests and Ethical Considerations

The authors state that they have no conflicts of interest to declare. Data sources used provided only de-identified, aggregate information. This study was not undertaken on the behalf of the Department of the Army or the Department of Defense.

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